Remarks/Arguments

Claims 1-15, 17 and 19-23 are pending in the application. Claims 1-9 and 15 have been withdrawn from consideration pursuant to a lack of unity objection. Claims 19-23 are new. Claims 10-14, and 19-23 are therefore under consideration. Reconsideration is requested in view of the above changes and the following remarks.

Claims 10 and 11 have been amended to remove the previously added wording which defined that the antigenic peptide fragment which is complexed to the heat shock protein is not derived from a heat shock protein.

Claim 19 finds basis in the description at page 8, line 28 and 29. Claims 20 and 21 find basis in the description at page 8, line 31. Claim 22 finds basis in the description at page 9, lines 8-11. Claim 23 finds basis at page 3, lines 23-27.

Response to Rejection Under 35 USC 112

Claims 10-14 and 17 have been rejected for allegedly reciting new matter. While applicants do not agree, the allegedly offending wording has been removed from the claims, thereby overcoming the rejection.

Response to Rejections Under 35 U.S.C. § 102

Phipps et al. (1991, EMBO J., 10:1711-1722) – Rejection Under 35 U.S.C. § 102(b)

Examiner has maintained the rejection of claims 10-14 and 17 as allegedly anticipated by Phipps *et al.* ("Phipps") in light of intrinsic evidence provided in the form of Swiss-Prot Accession number O59663. Applicant respectfully submits that the claims are not anticipated by Phipps, for the following reasons.

Examiner refers to figure 10 of Phipps and to the fact that this shows an immunoblot where polyclonal antibodies are directed to "*... the ATPase and Heat shock protein complex*". Examiner continues "*Phipps et al. teach that one of the bands is an about 60 kd molecular weight protein*", referring to page 1717 of Phipps. Examiner concludes that "*Therefore the complex of Phipps et al comprises a heat shock protein complex formed through complexing with*

a peptide fragment of the whole ATPase with the active binding site of the heat shock protein, the ATPase being immunoreactive with antibodies directed to both the Heat shock protein and the ATPase of the complex".

Applicant respectfully submits that Examiner's interpretation of what the Phipps document teaches is incorrect. Specifically, Phipps teaches a cylindrical protein complex (abstract, line 1). The structure of this complex is not completely defined, but based on the analysis performed and detailed by Phipps, it is taught in the Phipps paper that the complex is in the form of "*two stacked rings of eight subunits each; the rings enclose a central channel*". The complex *"is composed of equal quantities of two polypeptides of Mr 56,000 and 59,000*" (abstract). Lastly, the complex is seen to exhibit ATPase activity (abstract).

Complex of the claims not taught by Phipps

The claims of the instant application define the endogenous complexes as requiring: (i) an induced heat shock protein derived from the extracellular pathogenic bacteria, and (ii) an antigenic peptide *fragment* also derived from the extracellular pathogenic bacteria. Phipps does not teach such features.

What Phipps does teach, as recited above, is a protein complex in the form of a large cylindrical protein complex which exhibits ATPase activity, even at high temperatures (abstract). The ATPase complex is composed of subunits, namely "*equal quantities of two polypeptides of Mr 56,000 and 59,000*" (abstract). The identity of these subunits is *not* definitively described in Phipps.

It is predicted by Phipps that at least one of the two contributory subunits of the complex is a heat shock protein-like protein (see discussion at page 1718, column 2, paragraph 1 where it is postulated that one of the bands shown in lane h of figure 10 of Phipps is GroEL, and therefore that the equivalent band shown in lanes a and b is a protein homologous to the E coli GroEL shown in lance h, as the bands in lanes a and b have a similar molecular weight and ATPase activity).

Further discussion of this issue at page 1720, column 1, paragraph 1 states that "*The above observations suggest a possible relationship between Pyrodictium ATPase and the groEL*

family of proteins. However, in light of the unique symmetry of the ATPase, it is unlikely that the detailed structure of the proteins is similar".

Hence, when Examiner makes the statement in the office action of August 17, 2010 that *"antibodies directed to both the Heat shock protein and the ATPase of the complex"*, this statement is factually incorrect. Specifically, Examiner is *incorrect* to refer to the "heat shock protein" *and* the "ATPase of the complex" as *different* entities which can *both* be bound by antibodies. Rather, they are *one and the same*. The heat shock protein is one of 2 subunits which forms the complex, this complex have enzymatic activity as an ATPase and hence being known as an ATPase complex.

Accordingly, when Examiner states at page 3 of the Office Action of August 17, 2010 that *"It is the position of the examiner that Phipps et al figure 10 is an immunoblot with antibodies directed to the ATPase and Heat shock protein complex"*, Applicant contends that this statement is not correct. There is no ATPase and Heat shock protein complex as they are one and the same; what Phipps discloses is a complex with ATPase activity, wherein one of the component subunits of that complex is a protein which is homologous (based of molecular weight similarity and ATPase activity) to the heat shock protein GroEL found in E. coli .

The complex of Phipps comprises 2 subunits which, as shown in figure 11 of Phipps, form the cylinder-like ATPase structure. Accordingly, Phipps discloses a complex formed of a plurality of *"two distinct subunits"* (page 1720, column 1, last paragraph, not a complex of an ATPase complexed to a heat shock protein.

No teaching in Phipps of a complex comprising a peptide fragment

Furthermore, there is no teaching in Phipps of a complex formed between a heat shock protein and an antigenic peptide *fragment* because there is no disclosure of such a fragment. The 60kDa fragment identified by Examiner in lanes a and b of Figure 10, and assumed by Examiner to be homologous to the GroEL band shown in lane h of figure 10 (on the basis of the molecular weight data provided in the Swiss-Prot reference cited by Examiner) would indicate a full protein, not a *fragment*, as required by the claims of the instant application.

It is worth noting that Phipps teaches that 2 peptide subunits bind to each other to form a complex which comprises *8* subunits. Such a complex is not consistent with the complex required by the claims. There is, in fact, no mention in Phipps of ATPase complex itself binding to any fragments, or to either of the component subunits binding to an antigenic peptide fragment.

Complex of Phipps not derived from an extracellular pathogenic bacteria

Further still, the claims of the instant application recite that the complexes are extracted from an extracellular pathogenic bacteria. The teachings of Phipps relate to *Pyrodictium occultum*, an archaebacteria. Phipps teaches at page 1711, column 1, first paragraph that "*Archaebacteria constitute a third domain of life...*" and that "*They are phylogenically distinct from both eubacteria and eukaryotes*". Phipps states that "*In this report we describe an abundant, novel cytoplasmic protein complex in Pyrodictium and other thermophilic archaebacteria which appears as a ring with eight-fold symmetry in electron micrographs*". Accordingly, the protein complexes of Phipps are not derived from an extracellular pathogenic bacteria, as required by the claims of the instant application, more specifically, Phipps does not teach of a complex comprising a heat shock protein derived from an extracellular pathogenic bacteria and an antigenic peptide fragment derived from an extracellular bacteria.

For these reasons, it is therefore respectfully submitted that the teachings of Phipps do not anticipate the claims of the instant application.

Ferrero *et al* (Proc. Natl. Acad. Sci. USA) – Rejection Under 35 U.S.C. § 102(b)

Examiner has maintained the rejection of claims 10-14 as allegedly being anticipated by Ferrero *et al.* ("Ferrero") in light of evidence provided by Schumann (2000). Applicant respectfully submits that claims are not anticipated by these references.

Examiner states that "*It is the position of the examiner that the Heat shock protein does not form a complex with the entire urease protein, but with an antigenic fragment of a urease subunit*".

Ferrero is concerned with conferring protective immunity against gastric infection, by administering recombinant peptides. Ferrero considers 3 different proteins from Helicobacter pylori, namely (i) UreB – the B subunit of urease, (ii) HspB – a homolog to the heat shock protein GroEL, and (iii) HspA – a 13kDa GroEL homolog.

No teaching of a protein complex

Ferrero produces recombinant versions of each of these proteins, termed MalE-HspA, MalE-HspB and MalE-UreB (see page 6499, column 2, last paragraph). These recombinant proteins were then purified and then administered to animals. Table 2 shows the immunization schedule.

Ferrero states that "*Co-administration of recombinant H. pylori MalE-UreB and MalE-HspA antigens to mice resulted in 100% protection*". However, the important point to note here is that the HspA and UreB proteins were *co-administered*. They were not bound or complexed together and did not form a combined fusion protein.

This fact is further confirmed in the discussion section of Phipps at page 6502, column 1, paragraph 2, which states that "*In this study, we tested an antigenic preparation consisting of two recombinant proteins, H. pylori UreB and HspA...*".

HspA is homologous to GroEL: a protein with no peptide binding ability

As taught a page 6499, column 1 of Phipps, HspB is a 54 kDa protein encoded by the *hspB* gene. The HspB protein is homologous to the GroEL family of proteins. HspA has a molecular weight of 13 kDa and is encoded by the gene *hspB*. The HspA protein is homologous to the GroES family of proteins.

Phipps states at the last line of page 6499, column 1 to the first line of column 2 that "*Various investigators noted a physical association between urease holoenzyme and a protein that had a calculated molecular mass of 54-62 kDa. This protein was identified as being a homolog of the class of proteins ... to which GroEL belongs*". Accordingly, in the prior art, urease associates with GroEL (HspB). Hence, there is no teaching in Phipps, or reference in Phipps to the prior use of a complex between GroES and a urease subunit.

In fact, the skilled person, with knowledge of the 3D structure of the GroEL/GroES complex, would know that within that complex, GroEL defines an open cavity to which a peptide is bound, while GroES effectively acts as a "lid" to the complex. That is, GroES does not bind directly to the protein which is bound to GroEL. Rather, the binding of GroES to GroEL results in a confirmatory change of GroEL which results in changes to the protein bound thereto.

Accordingly, the skilled person, who would be aware of the structure and role of GroES, would know that GroES does not bind peptides. Accordingly, GroES (or in the case of the Phipps paper, HspA) would not bind directly with the UreB subunit to form a protein complex.

Accordingly, Examiner's assertion that Ferrero teaches of a complex between an antigenic peptide fragment and an antigenic peptide fragment of a urease subunit is unfounded. There is no such teaching in Ferrero, nor any pointer to the skilled person to make such a complex.

For these reasons, it is respectfully submitted that there is no disclosure in Ferrero which anticipates claims 10-14.

Examiner further refers to Dunn et al. (1990, Journal of Biological Chemistry). This document is taken to show the characteristics of subunits of Helicobacter urease. However, as stated above, Ferrero teaches of no complex between a heat shock protein of Helicobacter pylori and the Urease B subunit. Accordingly, it is irrelevant as to what the molecular weight of the Urease B subunit may be; it will not bind to HspA and in the experiments of Phipps, UreB and HspA recombinant proteins we co-administered, rather than being conjoined for form a fusion protein or similar complex.

Ding et al (1995), Biochemistry, 34:14918-14931) – Rejection Under 35 U.S.C. § 102(b)

Examiner has rejected claims 10-11 on the grounds that these claims are allegedly anticipated by Ding *et al.* ("Ding"). Applicant respectfully submits that the claims are not anticipated by Ding, for the following reasons.

Ding relates to complexes of the chaperonin GroEL and the capsid protein of bacteriophage HK97.

Examiner submits that Ding discloses "a *Heat shock protein complex that forms in an ATP dependent manner between a GroELS/5mer or 6-mer peptide fragment of a 42 kda head subunit protein of a bacteriophage*".

However, the teaching of Ding does not anticipate the subject matter of claims 10 and 11 as Examiner suggests. Both claims 10 and 11 require that *both* the heat shock protein and the antigenic peptide fragment of the claimed endogenous complexes be derived from the extracellular pathogenic bacteria.

A bacteriophage is not a bacteria. It is a virus which infects a bacteria. Accordingly, in the complex of Ding, the 5-mer or 6-mer peptide fragment is derived from the HK97 bacteriophage. That is, it is not derived from the extracellular pathogenic bacteria, as both claims 10 and 11 require.

Accordingly, neither claim 10, nor 11 is anticipated by the teachings of Ding.

Status of Application No. 10/363,454

The status of the '454 application, since the last action reported (an office action mailed February 19, 2010) is as follows. A response to the February 19, 2010 office action was filed. A further office action was issued on February 3, 2011. Applicant has not yet filed a response to the February 3, 2011 office action.

Copies of the office actions from the file of the '454 application are submitted herewith.

Status of Application No. 10/049,702

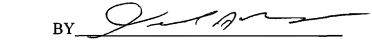
The status of the '702 application, since the last action reported (an office action mailed December 7, 2009) is as follows. A response to the December 7, 2009 office action was filed on June 7, 2010. A further office action issued on September 7, 2010. Applicant has not yet filed a response to the September 7, 2010 office action.

A copy of the September 7, 2010 office action from the '702 application was submitted in the present application under cover of an information disclosure statement on September 10,. 2010. Copies of all office actions from the file the '702 application prior to the September 7, 2010 office action are submitted herewith.

Conclusion

The claims remaining in the application are believed to be in order for allowance. An early action toward that end is earnest solicited.

Respectfully submitted
CAMILO ANTHONY LEO SELWYN COLACO

BY 

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